Polymyalgia Rheumatica: Recent Advances and Ongoing Questions

Written by Maria Vinall

Polymyalgia rheumatica (PMR) is the most common inflammatory rheumatic disease of the elderly; however, accurate diagnosis is difficult as symptoms often overlap with those of other rheumatic and inflammatory diseases. To date, the development of therapeutic approaches has been hindered by a lack of standardized classification criteria. Eric L. Matteson, MD, MPH, Mayo Clinic, Rochester, Minnesota, USA, reviewed the new provisional European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for the diagnosis of PMR [Dasgupta B et al. *Ann Rheum Dis* 2012].

EULAR and the ACR sponsored a joint study to establish classification criteria for PMR by assessing the performance of candidate criteria in an international, prospective, longitudinal study. A consensus conference and a wider Delphi survey were used to define candidate inclusion/exclusion criteria for classification of PMR. Assessments were made at baseline and at Weeks 1, 4, 12, and 26. A scoring algorithm was developed with and without ultrasound. Core inclusion criteria were >50 years of age with bilateral shoulder and/or pelvic girdle pain of abrupt onset and lasting for >2 weeks, morning stiffness of ≥45 minutes, and elevated C-reactive protein/erythrocyte sedimentation rate (ESR). The study comprised 125 PMR candidate subjects and 169 comparison subjects with conditions mimicking PMR (49 with rheumatoid arthritis, 29 with new-onset seronegative arthritis or connective tissue disease, 52 with shoulder conditions, and 39 with other conditions).

Using univariate logistic regression models, the investigators developed a scoring algorithm to identify patients with PMR based on clinical criteria (morning stiffness >45 minutes, hip pain or limited range of motion, absence of rheumatoid factor and/or anticitrullinated protein antibody, and absence of peripheral joint pain) and optional ultrasound (Table 1). The scoring scales are 0 to 6 points without ultrasound and 0 to 8 points with ultrasound. In the absence of competing diagnoses, a score ≥4 without ultrasound or ≥5 with ultrasound is indicative of PMR. In addition, patient-reported outcome measures, including modified Health Assessment Questionnaire, morning stiffness, the physical component of the Short Form-36, and the fatigue visual analog scale perform well in assessing disease activity in PMR and correspond to changes in inflammatory markers. These new criteria have been shown to have higher sensitivity [Macchioni P et al. ACR 2011 Presentation 1516] and specificity [Macchioni P et al. ACR 2011 Abstract 2347] compared with existing PMR classification criteria.

Table 1. Classification Criteria Scoring Algorithm for Polymyalgia Rheumatica.

	Points without US (0-6)	Points with US (0-8)*
Morning stiffniess >45 minutes	2	2
Hip pain or limited range of motion	1	1
Absence of RF or ACPA	2	2
Absence of other joint involvement	1	1
At lease 1 shoulder with subdeltoid bursitis and/ or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis	Not applicable	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis	Not applicable	1

ACPA=anticitrullinated protein antibody; RF=rheumatoid factor; US=ultrasound. *Optional ultrasound criteria.
Adapted from Dasgupta B et al. 2012 Provisional Classification Criteria for Polymyalgia Rheumatica: A European League Against Rheumatism/American College of Rheumatology Collaborative Initiative. *Ann Rheum Dis* 2012;71(4): 484-92.

Independent Peer-Reviewed Highlights about the

American College of Rheumatology 76th Annual Scientific Meeting

Giant cell arteritis (GCA), often associated with PMR, is an inflammatory disease that involves the arteries, and it usually affects the aorta, its branches, and/or the branches of the carotid and vertebral arteries [Jennette CJ et al. *Arthritis Rheum* 2013. In press]. Maria C. Cid, MD, University of Barcelona, Barcelona, Spain, discussed how these two disease syndromes overlap.

Both diseases occur more often in white females aged >50 years and are associated with the human leukocyte antigen DRB1*04 gene—particularly GCA. Marked acute-phase response, dramatic initial response to steroids, relapsing course and response to immunosuppressive or biologic agents tested are some of the shared clinical features. PMR and GCA have similar immunologic abnormalities, including elevated circulating interleukin (IL)-6 cytokine and soluble IL-2 receptors [reviewed in Matinez-Taboada VM et al. *Cytokine* 2008], a decrease in circulating regulatory T cells, an increase in circulating T helper 17 cells [Samson M et al. *Arthritis Rheum* 2012], and an increase in Toll-like receptor 7-expressing cells [Alvarez Rodriguez L et al. *Ann Rheum Dis* 2011], among others. Forty percent to 60% of patients with GCA have PMR, and PMR can occur following GCA [Martinez-Lado L et al. *Medicine (Baltimore)* 2011], while a more variable percentage (0 to 80) of patients with apparently isolated PMR have or will develop GCA depending on how and when GCA is defined.

The detection of GCA in PMR patients is best achieved with a temporal artery biopsy. Imaging in general is less sensitive and specific but may detect GCA in patients with predominant involvement of large vessels. In some patients with PMR, inflammatory involvement of the temporal artery is subtle. Whether molecular detection of inflammatory biomarkers in apparently normal temporal arteries may help in detecting incipient GCA in patients with PMR is not entirely clear [Corbera-Bellalta M et al. Unpublished]. Much remains to be discovered regarding the mechanisms that link these two conditions together and determine the course of this disease complex.

PMR does not cause structural damage, serious complications, or increased mortality but does have a major impact on quality of life [Hutchings A et al. *Arthritis Rheum* 2007]. According to Carlo Salvarani, MD, Arcispedale S. Maria Nuova, Reggio Emilia, Italy, who discussed the treatment options for PMR, the introduction of glucocorticoids (GCs) have had the biggest impact on treatment.

Studies based on patients referred to secondary or tertiary centers show GC treatment is needed from 2 to 5 years [Kyle V, Hazelman BL. *BMJ* 1990] and only 24% of patients stop GC treatment within 2 years [Kyle V, Hazleman BL. *Ann Rheum Dis* 1993], whereas population-based studies show that ~80% of patients stop treatment within 2 years [Chuang TY et al. *Ann Intern Med* 1982]. Discrepant results as to therapy discontinuation and relapse rate following PMR treatment suggest two different populations of patients with two different disease profiles: self-limiting disease requiring a shorter therapy period (12 months) and persisting disease requiring a longer therapy period (23 months).

Although effective, treatment with GCs is associated with high adverse event (AE) rates. In a population-based study, 65% of PMR patients treated with GCs developed at least 1 AE with age at diagnosis, cumulative dose, and female gender independently associated with an increased risk. Person-year analysis revealed that the risks of diabetes mellitus, vertebral fractures, femoral neck fractures, and hip fractures were 2 to 5 times greater among PMR patients compared with age- and sex-matched individuals from the same population [Gabriel SE et al. *Arthritis Rheum* 1997]. GC use is also associated with bone loss. Thus, bisphosphonate therapy should be initiated in high-risk patients [Grossman JM et al. *Arthritis Care Res* 2010]. Deflazacort was proposed to have less effect on bone mass versus prednisone; however, in at least one trial, no calcium-sparing properties were noted when compared with prednisolone [Krogsgaard MR et al. *Ann Rheum Dis* 1996]. Key points to keep in mind when using GC therapy include minimizing the initial dose and tapering slowly, recognizing that an isolated raise of ESR or CRP is not an indication for continuing/increasing GCs, and accepting that treatment must be flexible and tailored to the individual.

Results from randomized controlled trials using steroid-sparing agents (methotrexate, infliximab, and etanercept) are mixed [Ferraccioli G et al. *J Rheumatol* 1996; van der Veen MJ et al. *Ann Rheum Dis* 1996; Carporali R et al. *Ann Intern Med* 2004; Salvarani C et al. *Ann Intern Med* 2007; Kreiner F, Galbo H. *Arthritis Res Ther* 2010]. Results with methotrexate suggest that its ability to spare prednisone was lost in the long term. When added to prednisone, infliximab provided no benefit, but a steroid-sparing effect cannot be entirely ruled out [Salvarani C et al. *Ann Intern Med* 2007]. Short-term etanercept monotherapy may modestly improve disease activity in newly diagnosed GC-naïve patients [Kreiner F, Galbo H. *Arthritis Res Ther* 2010].

Studies are underway in PMR patients to examine the role of IL-6, and the use of tocilizumab as an IL-6 inhibitor, chronotherapy with modified-release prednisone, leflunomide, and the anti-CD20 monoclonal antibody rituximab.